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Review

Animal models of human cardiovascular disease, heart failure and hypertrophy

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Abstract

The progress made in our understanding of the pathophysiology and treatment of congestive heart failure (CHF) would not have been possible without a number of animal models of heart failure and hypertrophy, each one having unique advantages as well as disadvantages. The species and interventions used to create CHF depends on the scientific question as well as on factors such as ethical and economical considerations, accessibility and reproducibility or the model. How closely the model should mimic the human syndrome of CHF depends on the scientific question under investigation. If the goal is to study pathophysiological processes like remodeling or the function of subcellular systems such as excitation contraction-coupling processes, contractile protein function or energetics, the model of heart failure should mimic the clinical setting as closely as possible. However, if defined causal connections are under investigation such as structure–function analyses or regulation of gene expression, exact reflection of the clinical setting by the animal model may be less important. In this review, animal models of heart failure are discussed with particular focus on similarities between the animal model and the failing human heart regarding myocardial function as well as molecular and subcellular mechanisms. In addition, new models of heart failure and hypertrophy, and finally some recent animal models of myocarditis are reviewed.

Keywords: Hypertrophy; Heart failure; Animal models; Calcium

1. Introduction

During the last decade, considerable advances in our understanding and management of heart failure have been made. However, with increasing life expectancy and decreasing mortality of acute myocardial infarction and other conditions that may cause heart failure, the incidence, prevalence, mortality and economic costs of the disease are steadily increasing. The overall prevalence of congestive heart failure (CHF) is 1 to 2% in middle-aged and older adults, reaches 2 to 3% in patients older than age 65 years, and is 5 to 10% in patients beyond the age of 75 years [1]. Survival of patients suffering from heart failure depends on the duration and severity of the disease, on gender, as well as on therapeutic strategies. In the Framingham study, the overall 5-year survival rates were 25% in men and 38% in women [2]. In recent clinical trials with selected patients under state-of-the-art medical therapy, 1 year mortality ranged between 35% in patients with severe congestive heart failure (NYHA IV) in the Consensus trial [3] to 9 and 12% in patients with moderate CHF (NYHA II–III) in the second Vasodilator Heart Failure Trial [4] and the Studies of Left Ventricular Dysfunction (SOLVD) trial [5]. Mechanisms of death include sudden death in about 40%, worsening of heart failure in about 40% and other factors in 20% of the patients.

2. What are the characteristics of human heart failure?

Human heart failure has many underlying causes, the frequencies of which have changed considerably during the last decades. At present, the leading cause is coronary heart disease which accounted for 67% of CHF cases in

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the 1980s according to the Framingham heart study [2]. Most of these patients also had a history of arterial hypertension (57%). Valvular heart disease underlies failure in about 10% of the patients, and 20% of heart failure cases are attributable to primary myocardial diseases, of which dilated cardiomyopathy predominates. Regardless of the original cardiac abnormality, however, the advanced heart failure syndrome presents a complex picture including disturbed myocardial function, ventricular remodeling, altered hemodynamics, neurohumoral activation, cytokine overexpression, as well as vascular and endothelial dysfunction.

2.1. Neurohumoral and cytokine activation

Independent of the etiology of heart failure, activation of the neurohumoral and the cytokine system seems to play a critical role in the prognosis in CHF [6–8]. Activation of the neurohumoral systems occurs stepwise and is organ specific. It was shown recently, that increased cardiac adrenergic drive precedes generalized sympathetic activation in patients with mild CHF [9]. This results from increased norepinephrine release and decreased norepinephrine reuptake and seems to be associated with early attenuation of cardiac and arterial baroreceptor control of sympathetic tone [10,11]. Similarly, atrial natriuretic peptide is activated early in heart failure, and it was shown that atrial natriuretic peptide is elevated in asymptomatic patients with left ventricular dysfunction [12]. Although activation of local renin–angiotensin systems may occur early, plasma-renin activity and vasopressin release are only increased in patients with symptomatic heart failure [12].

Recent studies have identified the importance of cytokines as mediators of disease progression by mechanisms including necrotic and/or apoptotic myocyte cell death, myocardial fibrosis, and depression of myocardial function (for review see [13]). The influence of the vasoconstrictor peptide, endothelin has been extensively investigated. Both mature endothelin-1 and its precursor, big endothelin-1, are increased in the peripheral circulation in relation to the hemodynamic and functional severity of heart failure, and plasma levels of big endothelin-1 are correlated with the prognosis of patients with heart failure [14]. Similarly, circulating levels of tumor necrosis factor-α (TNF), of TNF receptors and of interleukin-6 are increased and positively related to the severity of heart failure [8]. TNF is expressed in the failing but not in the nonfailing human heart whereas TNF receptors (TNFR1 and TNFR2) are expressed in failing and nonfailing myocardium [7].

2.2. Hemodynamic abnormalities

Hemodynamic abnormalities in patients with advanced congestive heart failure include elevated filling pressures, reduced cardiac output and increased pulmonary and systemic vascular resistance. There is considerable evidence that endothelial dysfunction contributes to altered hemodynamics during rest and particularly to altered hemodynamics during exercise (for review see [15]). Endothelial dysfunction appears to result from remodeling of resistance arterioles and capillaries, from increased synthesis of endothelin, and from decreased synthesis of nitric oxide [16,17].

2.3. Myocardial alterations

At the level of the myocardium, characteristic functional, biochemical and molecular alterations occurring in end-stage heart failure have been described. Several studies have suggested that disturbed excitation–contraction coupling processes may underlie disturbed myocardial function [18–24]. This may be related to disturbed sarcoplasmic reticulum function due to decreased expression and activity of the sarcoplasmic reticulum calcium pump and increased expression and function of the sarcolemmal sodium–calcium exchanger (for review see [25]). In addition, disturbed energy metabolism may be involved in decreased sarcoplasmic-reticulum calcium transport [26].

Although myosin content may be decreased by about 20% due to replacement by connective tissue [18], maximum calcium-activated force was suggested to be similar in failing and nonfailing human myocardium [27,28]. This may be because force–time integral production of the individual crossbridge cycle is increased in the failing heart, associated with a reduced myofibrillar ATPase activity [18,29]. Previous studies suggested that unlike the situation in small mammals, alteration of crossbridge function may not be related to a myosin isoform shift, because it was observed that the ß-myosin heavy-chain isoform predominates in the left ventricle of nonfailing and failing human hearts [30]. This is in contrast to more recent studies in which at the level of mRNA ventricular expression of α-myosin heavy-chain isoform was observed in nonfailing hearts, which was decreased in failing human hearts [31,32]. Alternatively to a myosin isoform shift, the alteration in crossbridge function may, however, be related to changes in troponin T isoforms or alterations in myosin light chains [33,34]. Controversy exists regarding alteration of myofilament calcium sensitivity as measured in myofibrillar preparations which was suggested to be unchanged [35,36] or increased [37]. Wolff et al. suggested that calcium sensitivity is increased in failing myocardium from hearts with dilated cardiomyopathy which may be due in part to a reduction of protein kinase A-dependent phosphorylation of myofibrillar regulatory proteins [38].

Many studies have shown that the β-adrenergic signal transduction pathway is altered in the failing human heart. This results from a decrease in myocardial β1-adrenoceptor density which is partly due to decreased expression of the β1-adrenoceptor gene demonstrated both at the

mRNA and protein levels [39,40]. In addition, $G_{i\alpha}$ mRNA and protein concentrations are increased which may further inhibit adenylyl cyclase activity in failing human hearts [41].

Regarding extracellular matrix in human CHF, it was shown that connective tissue content is increased and that changes in collagen composition occur [42,43].

3. Animal models of heart failure and hypertrophy

During the period from 1993–1997, 1943 papers have been published on studies performed in animal models of heart failure (Table 1) and hypertrophy (Table 2). Most studies have been performed in rats with different interventions to induce hypertrophy and heart failure.

4. Rat models of heart failure

4.1. What are the advantages and disadvantages of using a rat model of heart failure?

Rat models are relative inexpensive and because of short gestation periods, a large sample size can be produced in a relatively short period of time. Therefore, rat models have been extensively used to study long-term pharmacological interventions including long-term survival studies [44,45]. However, there are several limitations to the use of rat models regarding differences in myocardial function compared to the human heart: (1) Rat myocardium exhibits a very short action potential which normally lacks a plateau phase [46]. (2) Calcium removal from the cytosol is predominated by the activity of the sarcoplasmic reticulum calcium pump whereas Na^+/Ca^{2+}-exchanger activity is less relevant [46,47]. (3) In normal rat myocardium, α-myosin heavy-chain isoform predominates and a shift towards the β-myosin isoform occurs with hemodynamic load or hormonal changes [48]. (4) Resting heart rate is five times that of humans and the force–frequency relation is inverse [46].

4.2. Rat coronary ligation model

Myocardial infarction following coronary artery ligation in Sprague–Dawley rats is a widely used rat model of heart failure. If the left coronary artery is not completely ligated, heart failure may occur as a consequence of chronic myocardial ischemia [49]. Complete occlusion of the left coronary artery results in myocardial infarction of variable sizes with occurrence of overt heart failure after 3–6 weeks in a subset of animals with large infarcts. The impairment of left ventricular function is related to the loss of myocardium. Failure is associated with left ventricular dilatation, reduced systolic function and increased filling pressures [44,50]. The progression of left ventricular dysfunction and myocardial failure is associated with neurohumoral activation similar to that seen in patients with CHF [51–54]. In particular, it was shown that ACE activity in the left ventricle correlated inversely with left ventricular function and that ACE activity in the kidney was only increased late after the induction of heart failure [55]. Depressed myocardial function is associated with altered calcium transients [56]. The density of L-type calcium channels, as evaluated by antagonist binding was shown to be decreased in moderate to severe stages of congestive heart failure [57,58]. Furthermore, it was shown that after 4, 8 and 16 weeks following coronary artery ligation, SR-Ca^{2+}-ATPase mRNA and protein levels decrease continuously with increasing severity of congestive heart failure. Interestingly, SR-Ca^{2+}-ATPase activity was found to be more depressed than expected from the reduction in protein levels [59].

Although a high initial mortality and induction of mild failure in most cases may be a disadvantage of this model it seems to be very useful for long-term studies of pharmacological interventions on the neurohumoral activation.

Of note, it was recently shown that ligation of the left descending coronary artery in Lewis inbred rats produces a uniformly large infarct with low mortality. This model, therefore, may be of advantage over the Sprague–Dawley rat model [60].

4.3. Rat aortic banding

Suprarenal aortic coarctation results in a very short reactive hyperreninemia of less than 4 days. Thereafter, the circulating renin–angiotensin system is no longer activated, but the ventricular ACE activity begins to rise. After a period of several weeks, ventricular ACE activity may decrease again to normal values which may be related to normalization of wall stress with increasing hypertrophy [61]. Numerous studies have been performed using aortic banding in rats to evaluate different aspects of left ventricular hypertrophy. Furthermore, after several months, a subset of animals goes into failure. In a recent study, chronic experimental aortic constriction imposed by banding of the ascending aorta in weanlings resulted in compensated left ventricular hypertrophy of the adult rats for several weeks. After 20 weeks of aortic banding two distinct groups could be identified: rats without change in LV systolic pressure development and those with a significant reduction in left ventricular systolic pressure [62]. The latter group exhibited increased left ventricular volumes, reduced ejection fraction and clinical signs of overt heart failure [63]. Left ventricular hypertrophy and failure was associated with increased β-myosin heavy chain mRNA and atrial natriuretic factor mRNA. Interestingly, a decrease in SR-Ca^{2+}-ATPase mRNA levels by the polymerase chain reaction occurred in left ventricular myocardium from failing animals after 20 weeks of banding but

Table 1
Animal models of heart failure

Species and technique	Selected references	Comments
Rat	1028[a]	
Coronary ligation	[44,49,59,60]	Clinical characteristics similar to human CHF; survival studies
Aortic banding	[62–64]	Studies of transition from hypertrophy to failure; survival studies
Salt-sensitive hypertension	[66,67]	Studies of transition from hypertrophy to failure
Spontaneous hypertension	[68–71]	Extracellular matrix changes; apoptosis; studies of transition from hypertrophy to failure
SH–HF/Mcc-facp	[72–76]	Altered NOS expression; altered calcium triggered calcium release
Aorto-caval fistula	[184,185]	Left ventricular hypertrophy; moderate LV dysfunction
Toxic cardiomyopathy	[186–189]	Decreased myocardial performance; myocyte loss with chronic ethanol application. Cardiomyopathy following catecholamine infusion or associated with *Diabetes mellitus*
Dog	148[a]	
Pacing tachycardia	[79–89,100–106]	Studies of remodeling and neurohumoral activation; studies on molecular mechanism of subcellular dysfunction; no hypertrophy
Coronary artery ligation	[111–115]	Studies on progression of heart failure; high mortality and arrhythmias
Direct-current shock	[115]	Studies of neurohumoral mechanisms
Volume overload -aorto-caval fistula -mitral regurgitation	[116–120]	Studies of neurohumoral mechanisms and therapeutic interventions
Vena caval constriction	[189]	Low cardiac output failure
Toxic cardiomyopathy	[190]	Left ventricular dysfunction
Genetic	[98]	Spontaneous cardiomyopathy in Doberman Pinscher dogs
Pig	43[a]	
Pacing tachycardia	[107–110]	Comparable with dog model for most aspects
Coronary artery ligation	[191]	Congestive heart failure; altered myocardial energetics
Rabbit	43[a]	
Volume and pressure overload	[122–126]	Myocardial alterations similar to failing human myocardium
Pacing tachycardia	[127–131,192]	Myocardial alteration similar to failing human myocardium
Toxic cardiomyopathy	[132]	Studies of functional consequences of altered ryanodine receptors
Guinea pig	31[a]	
Aortic banding	[134,135,193]	Myocardial function and alteration of calcium handling similar to human heart failure
Syrian hamster	10[a]	
Genetic	[136–147]	Hypertrophy and failure; alterations critically dependent on strain and age
Cat	11[a]	
Pulmonary artery constriction	[194,195]	Transition from compensated right ventricular hypertrophy to failure
Turkey	9[a]	
Toxic cardiomyopathy	[196]	Alteration of calcium handling and myocardial energetics
Bovine	25[a]	
Genetic	[197]	Similar to human heart failure regarding changes in β-adrenergic system
Sheep	17[a]	
Pacing tachycardia	[198,199]	Similar to dog and swine model of pacing tachycardia
Aortic constriction	[200]	Transition from compensated hypertrophy to left ventricular dysfunction

[a] Total number of references in this species (failure and animal species) 1993–1997.

Table 2
Animal models of hypertrophy

Species and technique	Number of references 1993–1997	Selected references
Rat	1082	
Aortic constriction		[62,63]
Pulmonary artery constriction		[201]
Hypertension		
-Renal ischemia		[202]
-DOCA		[203]
-Dahl salt-sensitive		[66,67]
-SHR		[68,69]
Arteriovenous fistula		[204]
Hyperthyroidism		[205]
Hypoxia		[205]
Catecholamines		[205]
Exercise		[206,207]
Rabbit	96	
Aortic insufficiency/constriction		[122–124]
Pulmonary constriction		[121]
Hyperthyroidism		[121]
Dog	75	
Aortic constriction		[208]
Valvular aortic stenosis		[209]
Tricuspid regurgitation		[210]
Pig	67	
Pulmonary artery constriction		[211]
Cat	24	
Pulmonary artery constriction		[194]
Hamster	28	
Genetic		[136]
Ferret	9	
Pulmonary artery constriction		[212,213]
Sheep	26	
Aortic constriction		[214]
Baboon	3	
Hyperthyroidism		[215]
Renal ischemia		[216]
Guinea pig		
Aortic constriction		[193,133–135,217]
Mouse	165	
Renal ischemia		[218]
Exercise		[219]
Aortic constriction		[220]
Transgenic animals		see Table 3

not in nonfailing hypertrophied hearts. From this data, it was suggested that the decrease in SR-Ca^{2+}-ATPase mRNA levels may be a marker of the transition from compensatory hypertrophy to failure in these animals [62]. During compensated hypertrophy, while catecholamine levels are normal, there is activation of the local myocardial renin–angiotensin system, which may be important for the development of myocardial failure [64]. With the development of heart failure, plasma catecholamine levels can increase [65].

This model seems to be well suited for studying the transition from hypertrophy to failure at the level of the myocardium. Nevertheless, one should keep in mind that considerable differences in the function of subcellular systems exist between rat and human myocardium [46].

4.4. Dahl salt-sensitive rats

Another animal model which may be suited to study the transition from compensated hypertrophy to failure is the Dahl salt-sensitive rat [66,67]. This strain of rats develops systemic hypertension after receiving a high-salt diet. This

results in concentric left ventricular hypertrophy at 8 weeks, followed by marked left ventricular dilatation and overt clinical heart failure at 15–20 weeks. Failing rats die within a short period of time. Heart failure is associated with reduced myocardial performance as shown in isolated muscle strip preparations [67].

4.5. Spontaneous hypertensive rats (SHR)

The spontaneous hypertensive rat (SHR) is a well-established model of genetic hypertension in which cardiac pump function is preserved at 1 year of age [68]. At 18–24 months, cardiac failure develops which includes reduced myocardial performance and increased fibrosis. In this model, although altered calcium cycling was observed, no decrease in mRNA of the sarcoplasmic reticulum calcium pump was found during the transition from compensated hypertrophy to failure [69,70]. It was suggested that the transition to failure is associated with significant alterations in the expression of genes encoding extracellular matrix [70]. Furthermore, an increased number of apoptotic myocytes was observed, and it was suggested that apoptosis might be a mechanism involved in the reduction of myocyte mass that accompanies the transition from stable compensation to heart failure in the model. Interestingly, the angiotensin-converting enzyme inhibitor captopril was associated with reduction in the exaggerated apoptosis that accompanied CHF [71].

4.6. SH–HF rats

Spontaneously hypertensive rats which develop failure before 18 months of age have been selectively bred (SH–HF). Development of heart failure occurs earlier in SH–HF rats which carry the *facp* (corpulent) gene, which encodes a defective leptin receptor (SH–HF/Mcc-facp) [72]. In these animals, renin-plasma activity, atrial natriuretic peptide, and aldosterone levels progressively increase with age, and renin-plasma activity is independently correlated to cardiac hypertrophy [73]. Interestingly, hearts from the SH—HF rat exhibit a more negative force–frequency relationship than control rats [74]. In a recent study performed in SH–HF, Gómez at al. suggested that calcium current density, density and function of ryanodine receptors, and sarcoplasmic reticulum calcium uptake are normal. However, they showed that the relationship between calcium current density and the probability of evoking a spark was reduced indicating that calcium influx is less effective at inducing SR calcium release. It was speculated that these changes may be related to spacial remodeling between L-type calcium channels and ryanodine receptors [75]. Of note, a recent report showed that Ca^{2+}-dependent NOS activity and expression of endothelial NOS is increased in hypertensive SH–HF rats [76].

5. Dog models of heart failure

5.1. What are the advantages and disadvantages of using dog models of heart failure?

Generally, dog and other large animal models of heart failure may allow the study of left ventricular function and volumes more accurately than rodent models. In particular, they better allow chronic instrumentation. Furthermore, in dog, like in human myocardium, the β-myosin heavy-chain isoform predominates and excitation–contraction coupling processes seem to be similar to the human myocardium [77]. The force–frequency relation, as evaluated by E_{max}, the slope of the end-systolic pressure–volume relation, was shown to be positive in autonomically intact awake dogs as well as during autonomic blockade [78]. On the other hand, dog models are costly and require substantial resources with respect to housing and care.

5.2. Chronic rapid pacing

Chronic rapid pacing at heart rates above 200 beats per minute in previously healthy dogs within several weeks produces the syndrome of congestive heart failure [79–81]. In the majority of studies, chronic pacing tachycardia results in progressive biventricular chamber dilatation over a 3–4 week period. This is associated with a significant decrease in ejection fraction and diastolic dysfunction, followed by decreased cardiac output and increased systemic vascular resistance [80,82,83]. It is important to note that the changes in LV geometry and function are not accompanied by significant changes in LV mass and hypertrophy [80,81]. In addition, heart failure has been shown to be reversible with respect to clinical, hemodynamic and neurohumoral abnormalities when pacing is stopped [84]. The exact pathogenesis in this model is still unclear.

Similar to human heart failure, there are time-dependent changes in neurohumoral activation with an early sympathetic activation, increase in catecholamine plasma levels and attenuation of parasympathetic tone [85,86]. In addition plasma ANP levels are elevated early in the development of left ventricular dysfunction [87]. Systemic activation of the renin–angiotensin system is seen with progressive pump failure [86,88]. Furthermore, endothelial dysfunction with decreased agonist-stimulated and flow stimulated nitric-oxide mediated coronary vasodilation has been observed similar to the situation in patients with heart failure [89].

Consistent with the findings in failing human hearts, force–frequency relation is blunted or inversed in the pacing tachycardia failure dog model [90,91]. Altered force–frequency relation in this model was also observed at the level of the isolated myocyte [92]. Komamura et al. observed that failing animals do not further augment stroke volume by an acute increase in preload, suggesting that the

Frank–Starling reserve is exhausted under in vivo conditions [93].

At the level of the myocardium, contractile force has been shown to be decreased and calcium transients were prolonged [94]. Furthermore, Zile et al. showed that relaxation is impaired in isolated myocytes from failing hearts [95].

This may be related to altered expression and function of calcium-handling proteins. Although, an earlier report suggested that SR-Ca^{2+}-ATPase mRNA levels measured in left ventricular endocardial biopsies at baseline and at the onset of pacing tachycardia-induced failure do not significantly change [96], more recent data indicates that expression of SR-Ca^{2+}-ATPase is decreased. Similar to changes that occur in the failing human heart, O'Rourke et al. recently reported that mRNA and protein levels of sarcoplasmic reticulum calcium ATPase are decreased and that mRNA and protein levels of the sarcolemmal Na^{+}/Ca^{2+}-exchanger are significantly increased [97]. The latter findings are consistent with measurements from Cory et al. showing a decreased activity of the SR calcium pump in mongrel dogs with pacing-induced heart failure and in Doberman Pinscher dogs with dilated cardiomyopathy [98]. Thus altered calcium handling may result from reduced SR calcium uptake and accumulation and increased calcium sequestration into the extracellular space. In addition, a decreased number of ryanodine receptors has been suggested in a study by Cory et al. [98]. Consistently, Vatner et al. showed that in the pacing tachycardia failure model, [^{3}H]ryanodine receptor binding is depressed. However, this depression occurred as early as 1 day after pacing and remained at this depressed level up to 4–7 weeks of pacing when heart failure was manifest [99]. In the same study, dihydropyridine binding was not altered in the failing animals [99].

Whether altered myofilament calcium sensitivity contributes to altered myocardial function in this model is not clear [100,101].

Considerable changes seem to occur in myocyte shape, in cytoskeleton and in the extracellular matrix. In contrast to findings in human heart failure, collagen content was shown to be decreased and its structure was altered which may result in decreased collagen support [102]. Changes in cytoskeleton and extracellular matrix were suggested to be a major factor for ventricular remodeling, and apoptotic cell death was also suggested to play a key role in the development of CHF [103,102].

Significant alterations have been observed in the β-adrenoceptor–adenylyl-cyclase system. These include decreased β-adrenergic receptor density [102]. Unlike the situation in human heart failure, mRNA levels of adenylyl-cyclase have been shown to be reduced consistent with reduced basal and forskolin-stimulated adenylyl cyclase activity [104].

Similar to human CHF, this model was shown to be associated with malignant arrhythmias and sudden cardiac death which may be related to prolongation of the action potential [105]. Interestingly, action potential prolongation could be reversed by adenovirus mediated transfer of potassium channels (AdShK) in isolated myocytes from failing dog hearts [106].

In summary, the pacing-tachycardia dog model seems very valuable for studying neurohumoral mechanisms and peripheral circulatory alterations, both of which closely resemble that observed in human heart failure. Furthermore, alterations in myocardial function and molecular changes in calcium-handling proteins underlying altered myocardial function show considerable similarities to the failing human heart. This may allow the study of the transition from a compensated state of left ventricular dysfunction to overt failure with respect to alterations in calcium homeostasis. The model also provides temporal and mechanistic information on left ventricular remodeling and allows the study of pharmacologic interventions to influence the remodeling process. The limitations of the rapid pacing model include an uncertain pathogenesis, and lack of long-term stability because heart failure is reversible when pacing is stopped. Furthermore, unlike clinical forms of CHF, the development of CHF by chronic rapid pacing is not associated with hypertrophy or increased collagen content. Loss of collagen support may considerably contribute to ventricular remodeling in this model.

The technique of tachycardia pacing to induced heart failure has also been used in pigs and sheep and findings similar to those in dogs have been observed with respect to clinical, hemodynamic and neurohumoral changes [107–110].

5.3. Coronary artery ligation and microembolization

Coronary artery ligation and microembolization have been used to produce myocardial infarction and CHF in dogs. In closed-chest dogs, approximately up to 7 embolization procedures are performed 1–3 weeks apart. Three months after the final microembolization, there are clinical signs of heart failure, there is left ventricular dilatation, decreased ejection fraction, and neurohumoral activation similar to that observed in humans [111]. A decreased number of β-adrenoceptors and L-type calcium channels have been observed 3 months after the final embolization procedure [112]. Furthermore, sarcoplasmic reticulum Ca^{2+}-ATPase activity and protein levels were reduced in left ventricular myocardium from failing animals [113]. With this model, the progression from left ventricular dysfunction to heart failure and the influence of pharmacological interventions can be studied [114].

The model has several disadvantages. Because of extensive collateral circulation, there are important differences in the pattern of infarction between the human and the dog. The model is time consuming, technically demanding and expensive. The model is associated with high mortality and with a high incidence of arrhythmias.

5.4. Transmyocardial direct-current shock

A number of transmyocardial direct-current shocks applied through a catheter into the left ventricular chamber in anesthetized dogs, results in left ventricular hypertrophy and dilatation, decreased ejection fraction and decreased cardiac output over a 4-months period [115]. This is associated with increased plasma catecholamines but with no change in plasma renin activity [115].

5.5. Volume overload

In dogs, volume overload has been produced by creation of an arteriovenous fistula or by destruction of the mitral valve [116,117]. Chronic experimental mitral regurgitation produced in closed-chest dogs by disruption of mitral chordae or leaflets using an arterially placed grasping forceps results in left ventricular hypertrophy and dilatation within 3 months and development of overt clinical heart failure occurs in this model [117]. Neurohumoral activation including local activation of the RAS was observed which is associated with depressed myocardial function [118–120]. The model has been used to study the influence of chronic β-adrenoceptor blockade on myocyte and left ventricular function which both significantly improved with this treatment [120].

6. Rabbit models of heart failure

6.1. What are the advantages and disadvantages of using a rabbit model of heart failure?

Rabbit models are less expensive than dog models. In addition, nonfailing rabbit myocardium exhibits interesting similarities to the human heart: (1) The β-myosin heavy-chain isoform predominates in adult animals, (2) the sarcoplasmic reticulum contributes by about 70% and the Na^+/Ca^{2+}-exchanger contributes by about 30% to calcium elimination, (3) the force–frequency relation is positive [121,46,47].

6.2. Volume and pressure overload

Volume overload, pressure overload and the combination of both are used to induce heart failure in rabbits. Chronic severe aortic regurgitation in rabbits, created by aortic valve perforation with a catheter, produces left ventricular hypertrophy, followed by systolic dysfunction and heart failure after a period of months [122]. Occurrence of heart failure is more consistently and rapidly observed when aortic regurgitation is combined with aortic constriction. In the model developed by Ezzaher et al., aortic insufficiency is produced by destroying the aortic valve with a catheter introduced through the carotid artery. After 14 days, aortic constriction is performed just below the diaphragm. Heart failure occurs about 4 weeks after the initial procedure [123,124]. Heart failure is associated with alterations in the β-adrenoceptors system similar to those in humans [123]. Furthermore, in this model there is inversion of the force–frequency relation and alteration of post-rest potentiation which closely resembles the situation in the human heart [125]. Interestingly, protein and mRNA levels of Na^+/Ca^{2+}-exchanger were significantly increased in failing compared to nonfailing animals whereas sarcoplasmic reticulum Ca^{2+}-ATPase was not significantly altered [126]. This may indicate that increased transsarcolemmal calcium loss by increased Na^+/Ca^{2+}-exchanger activity my decrease calcium availability to contractile proteins and decrease myocardial function even without direct alteration of sarcoplasmic reticulum function.

Because this model closely mimics alterations of myocardial function observed in the end-stage failing human myocardium, this model may be well suited to study alterations in excitation–contraction coupling processes occurring during the transition from compensated hypertrophy to failure.

6.3. Tachycardia-pacing

Recently, chronic rapid pacing at rates between 350 and 400 beats per minute over a period of several weeks in rabbits was shown to produce myocardial depression as well as clinical, hemodynamic and neurohumoral signs of heart failure [127–129]. Regarding myocardial function, force–frequency relation was severely depressed and inverted at higher stimulation rates [130]. This is similar to the alteration of the force–frequency relation observed in failing human hearts. As was observed in the tachycardia-pacing dog failure model, no left ventricular hypertrophy is developed in the rabbit model. Interestingly, Eble et al. recently showed that although the rate of myosin heavy chain (MHC) synthesis was increased, left ventricular MHC content was not increased [131]. The authors suggested that accelerated degradation may contribute to the failure of myocardial hypertrophy in this model [131]. These findings may also be relevant for pathophysiology of tachycardia-pacing induced CHF in other animal species

6.4. Doxorubicin cardiomyopathy

Doxorubicin exhibits acute and chronic cardiotoxicity and has been used to induce failure in various animal species. Several different mechanisms involved in the pathophysiology of doxorubicin-induced heart failure have been suggested including free radical generation and lipid peroxidation, reactive sulfhydryl groups, binding to channel regulatory sites, or inhibition of mRNA and protein synthesis [132].

In a recent study, doxorubicin, given intravenously twice weekly for 6–9 weeks resulted in myocardial failure, the

degree of which was correlated with decreased [^{3}H]ryanodine binding. Furthermore a decreased number of ryanodine receptors was indicated from Western Blot data. These findings may suggest that this model is suited to study functional consequences of altered ryanodine receptor expression [132].

7. Guinea pig models

7.1. Aortic banding

Following 8 weeks of banding of the descending thoracic aorta in guinea pigs, overt heart failure develops in a subgroup of animals [133–135]. Alteration of myocardial function in this guinea pig model has some similarities with end-stage failing human myocardium. Siri et al. showed that the force–frequency relation is blunted in isolated myocytes from failing hearts [133]. Furthermore, a decrease in SR-Ca^{2+}-ATPase protein levels and phospholamban protein levels was observed in failing guinea pig hearts following 8 weeks of banding of the descending thoracic aorta as compared to an age-matched banded group without clinical signs of heart failure [134]. Regarding myosin isoforms, guinea pig myocardium, like the human ventricular myocardium, contains predominantly the β-myosin heavy chain with small amounts of α-myosin. This is shifted completely to β-myosin without any α-myosin heavy chain present in hypertrophied and failing hearts [135].

These studies show that this guinea pig model has similarities to human heart failure with respect to calcium cycling, myosin isoforms and myocardial function. This model may be suited to study the transition from cardiac hypertrophy to failure with respect to alterations in excitation–contraction coupling systems.

8. Syrian hamster

8.1. Cardiomyopathic hamster

Cardiomyopathic strains of the Syrian hamster have been widely used as a model for cardiac hypertrophy and heart failure [136]. The model exhibits an autosomal recessive mode of inheritance [136,137]. The cardiac disease proceeds progressively in several histologic and clinical phases during the life of the animal and overt heart failure develops after 7–10 months. Histologically, necrotic, calcified myocardial lesions are observed initially in the development of the disease. Microvascular spasms and disturbed calcium handling have been suggested to be relevant for the pathophysiology in this model and beneficial effects of verapamil have been observed [138–140]. The density of L-type calcium channels seems to be increased in younger animals before morphological evidence for the myopathy is present, however, when there is fully developed myopathy, there seems to be no appreciable difference between control and myopathic hamsters [141,142]. Kuo et al. showed decreased gene expression of sarcoplasmic reticulum calcium pump in Syrian hamsters. Interestingly, this alteration in gene expression preceded any noticeable myocyte damage [143]. On the other hand, Whitmer et al. observed that sarcoplasmic reticulum calcium uptake is decreased in 9-month-old animals exhibiting heart failure but not in hypertrophic hearts without signs of heart failure [140]. Enhanced activity of the Na^+/Ca^{2+}-exchanger in failing animals was recently suggested from electrophysiological measurements [144]. Furthermore, time-dependent changes in myosin isoform expression has been observed [145].

Recently, a genetic linkage map localized the cardiomyopathy locus on hamster chromosome 9qa2.1-b1 [146]. Furthermore, it was shown that the cardiomyopathy results from a mutation in the delta-sarcoglycan gene [147].

In summary, the advantages of this model are (1) absence of surgical manipulations, (2) low costs and (3) the ease with which large numbers of animals can be studied. It is important to state that there are differences among the strains, and in the time course of the pathologic changes, and therefore, the time point at which measurements are performed is critically important in this model. Furthermore, subcellular alterations underlying myocardial failure seem to be different from those in failing human hearts.

9. Recent models of CHF in mice

The recent development of techniques to alter specifically the expression of genes greatly improved our understanding of the pathophysiology of heart failure. Moreover, several genetic models of heart failure by addition or deletion of genes in mice have been developed and miniaturized physiological techniques to evaluate the resulting cardiac phenotypes have been established [148,149]. These models allow the identification of genes that are causative for heart failure and to evaluate molecular mechanisms responsible for the development and progression of the disease (Table 3).

Gene-targeted disruption of the muscle LIM protein (MLP) in mice is a new model of dilated cardiomyopathy and heart failure [150]. MLP is a regulator of myogenic differentiation. Mice which are homozygous for the MLP knockout develop dilated cardiomyopathy associated with myocardial hypertrophy, interstitial cell proliferation and fibrosis. Adult mice show clinical and hemodynamic signs of heart failure similar to those in humans. Because of these similarities, it was suggested that molecular mechanisms resulting in MLP dysfunction may be involved in

Table 3
Transgenic models of heart failure and hypertrophy

Intervention	Phenotype	Reference
Gene overexpression		
C-myc	Myocardial hyperplasia	[221]
Epstein-Barr virus nuclear antigen	Dilated cardiomyopathy	[157]
Polyomavirus large T-antigen	Cardiomyopathy	[158]
Calmodulin	Myocardial hypertrophy and hyperplasia	[166]
Myogenic factor 5	Cardiomyopathy and failure	[151]
$G_{s\alpha}$	Cardiomyopathy and failure	[152]
α_1-Adrenergic receptor	Myocardial hypertrophy	[168]
p21-ras	Myocardial hypertrophy; myofibrillar disarray	[222]
Interleukin β and interleukin β receptor	Hypertrophy	[167]
Nerve growth factor	Cardiomyopathy	[155]
Insulin-like growth factor 1	Cardiomyopathy; hyperplasia	[156]
β-adrenergic receptor kinase	Reduced contractility	[154]
G protein coupled receptor kinase	Reduced contractility	[223]
TGR (m Ren 2)27	Hypertrophy in rats	[224]
Gene mutation		
α-cardiac myosin heavy chain	Hypertrophic cardiomyopathy	[162]
Lack of β-myosin light chain binding domain	Hypertrophic cardiomyopathy	[163]
Knockout of gene		
Muscle LIM protein	Dilated cardiomyopathy and failure	[150]
Adenine nucleotide translocator	Hypertrophy	[169]
Transforming growth factor β	Myocarditis and failure	[182]
Interferon regulatory factor 1	Myocarditis and failure	[181]

the development of human dilated cardiomyopathy and CHF [150].

Development of cardiomyopathy was also observed in mice with knockout of myogenic factor 5 [151].

Another mouse model of dilated cardiomyopathy is overexpression of the cardiac stimulatory G protein α subunit ($G_{s\alpha}$). In this model, chronic sympathetic stimulation was suggested to be the cause of cardiomyopathy. Older mice exhibited left ventricular dilatation and dysfunction and increased mortality [152].

Transgenic mice overexpressing either β-adrenergic receptor kinase or G protein-coupled receptor kinase 5, resulting in uncoupling of the β-adrenergic receptors, also exhibit reduced contractility but without clinical signs of overt CHF [153,154].

Myocyte hyperplasia and dilated cardiomyopathy have been observed in animals with overexpression of the insulin-like growth factor 1 gene, and the nerve growth factor (NGF) [155,156].

Cardiomyopathy was also observed in a tropomodulin-overexpression model and in transgenic mice expressing Epstein-Barr virus nuclear antigen-leader protein or polyoma virus large T-antigen [157,158]. Tropomodulin is a component of the thin filament proteins which determines sarcomeric-actin filament length. A recent model of transgenic overexpression of tropomodulin exhibited dilated cardiomyopathy 2–4 weeks after birth with reduced contractile function and heart failure. This was associated with loss of myofibrillar organization [159].

10. Recent animal models of hypertrophy

Numerous animal models have been developed in the past and applied to study molecular mechanisms and functional aspects of myocardial hypertrophy (Table 2). Comparison of these models with different forms of myocardial hypertrophy in humans is difficult because unlike end-stage failing myocardium available from cardiac transplantation surgery, nonfailing hypertrophied human myocardium is not readily available.

Animal models of hypertrophy which allow the study of the transition from compensated hypertrophy to heart failure have been discussed in the sections above and hypertrophy associated with hypertension is addressed in the review by Pinto and Ganten [160]. Therefore, in the following section, only newer aspects of animal models of hypertrophy will be discussed.

10.1. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy is a complex cardiac disease in humans which is caused by a genetic malformation of the heart. The disease can be caused by a mutation in at least one of four genes that encode proteins of the cardiac sarcomere: the β-myosin heavy chain, cardiac troponin T, α-tropomyosin and myosin-binding protein C gene. In addition, mutations in the two genes encoding the myosin light chains that may cause a rare form of the disease, have been reported and other genes that cause the disease are likely to be found. Clinically the disease is characterized by asymmetrical left ventricular hypertrophy, myofiber disarray, diastolic left ventricular dysfunction, and increased incidence of sudden death. The clinical course varies markedly depending on the type of mutation and other unknown factors (for review see [161]).

A transgenic mouse model of the disease (a point mutation of the Arg^{403}-Gln in the α-myosin heavy-chain gene) has been developed which exhibits similarities to human familial hypertrophic cardiomyopathy [162]. A similar phenotype was recently observed in transgenic mice lacking the light chain binding domain of the β-myosin heavy chain [163]. These models will allow the

study of the still unknown pathophysiological mechanisms of the disease.

10.2. Transgenic models of hypertrophy

Other transgenic mice models of hypertrophy have been developed (Table 3). Overexpression of the H-*ras* gene targeted to ventricles with the MLC2v promotor causes ventricular hypertrophy including myofiber disarray, obstruction of the left ventricular outflow tract, and diastolic dysfunction [164,165].

Overexpression of calmodulin, a calcium-binding protein, can also induce cardiac hypertrophy in transgenic mice [166].

Hypertrophy was also induced in transgenic mice overexpressing interleukin 6 and the interleukin 6 receptor associated with activation of gp130, the latter was suggested to mediate hypertrophic response in this model [167].

Chronic activation of the α_1-adrenergic receptor pathway also results in hypertrophy in transgenic mice overexpressing the α_1-adrenergic receptor [168].

Recently, a mouse transgenic model for mitochondrial myopathy exhibiting skeletal muscle myopathy and cardiac hypertrophy has been reported. This model was created by knockout of the heart/muscle isoform of the adenine nucleotide translocator (Ant1) [169].

11. Recent animal models of myocarditis

Several animal models of myocarditis have been developed and progression to dilated cardiomyopathy and heart failure occurs in some of those [170–174]. Congestive heart failure develops after an acute phase of myocarditis induced by the M variant of the encephalomyocarditis virus [175]. Myocyte necrosis and biventricular dilatation occur during the phase of viremia, and signs of CHF were observed at 7 to 14 days after inoculation. Altered myocardial function is associated with neurohumoral activation. Potential mechanisms contributing to the progression of CHF include a persistence of the viral RNA within the myocardium, viral-mediated cytokine production with continued myocytolysis, a prolonged immune response, and continued fibrosis and abnormalities in microcirculatory function. Interestingly, tumor necrosis factor (TNF) was elevated in this model and an exogenously administered anti-TNF antibody improved survival and reduced the myocardial lesion, suggesting the importance of TNF in the pathogenesis [176].

Another widely used model is based on experimental autoimmune myocarditis [177]. This model has been applied to different species. The model resembles human giant cell myocarditis. It was shown that myocarditis and hemodynamic deterioration developed within 21 days after immunization of rats with cardiac myosin. This was associated with increased activity and expression of iNOS, and an inhibitor of iNOS effectively attenuated histopathological changes. Accordingly, it was concluded that NO may play an important role in mediating pathophysiological changes in myocarditis of autoimmune origin [177].

Autoimmune myocarditis has also been induced with various intracellular antigens. When CAF1/J mice were immunized with a monoclonal anti-dog sarcoplasmic reticulum, Ca^{2+}-ATPase antibody myocarditis developed [178]. Furthermore, myocarditis and decreased cardiac function was observed after immunization of guinea pigs with the isolated ADP/ATP carrier protein [179].

Recently, transgenic knockout models of different components of the immune system have provided useful insights in the pathogenesis of viral myocarditis (for review see [180]). An interesting mouse myocarditis model was established by knocking out the gene encoding the interferon regulatory factor-1. This factor plays an important role in the regulation of interferon expression. Inactivation of the gene in mice leads to a pronounced susceptibility to Coxsackie-viral myocarditis [181].

Knockout of the gene of transforming growth factor $\beta 1$ in mice was shown to result in severe perimyocarditis resembling viral myocarditis or autoimmune diseases [182,183].

12. Animal models of heart failure and hypertrophy in the past, present and future

Besides basic ethical and philosophical questions, the use of animal models of heart failure and hypertrophy needs careful consideration because of at least two reasons: (1) the disease may be associated with discomfort and pain to the animal, and (2) results from animal studies are not readily transferable to the situation in patients with heart failure.

In the past, a large number of studies have been performed in animals with overt clinical heart failure to evaluate pathophysiology from the level of the intact instrumented animal to the tissue homogenate. These kind of studies brought a lot of information on hemodynamics, neurohumoral activation, myocardial function and subcellular and molecular alterations in the failing heart. There are great differences between species and models and only some models mimic human heart failure in some aspects. These kind of studies seem to be less important in the presence because with recent invasive and noninvasive technologies hemodynamics can be studied in patients. Furthermore, with cardiac transplantation surgery, end-stage failing human myocardium became available for functional, biochemical and molecular biology studies allowing the evaluation of alterations which are present in end-stage failure in the human heart itself. However, it is rather difficult or impossible to study myocardial changes

during compensated, less-severe stages of CHF, during the transition from hypertrophy to failure or during the process of remodeling. Therefore, in order to study transition processes occurring in heart failure, animal models are critically important. Furthermore, animal models of heart failure may be relevant to study the effects of new pharmacologic strategies on hemodynamics, neurohumoral activation, and survival under preclinical conditions.

At present, transgenic animal models of hypertrophy and heart failure are critically important for understanding the molecular alterations underlying the development of the disease. Addition or deletion of genes in transgenic mice together with miniaturized physiological techniques to evaluate the resulting cardiac phenotypes allow the identification of genes that are causative for heart failure and to evaluate molecular mechanisms responsible for the development and progression of the disease. Hypertrophy and heart failure models in mice will be used in the future to study rescue or repair by knockout or overexpression of specific genes. Finally, animal models of heart failure which mimic distinct features of human heart failure will be critically important to the study of the consequences of gene transfer and molecular techniques to correct disturbed subcellular processes in the failing heart. These kind of studies are a prerequisite to the development and introduction of molecular strategies for the treatment of CHF in patients.

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